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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,557	10/31/2003	Samuel Jotham Reich	129402.00801	7768

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EXAMINER	
MCGARRY, SEAN	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/699,557	REICH ET AL.	
	Examiner	Art Unit	
	/Sean R. McGarry/	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *1-32,46,51,52,55,56,58-60,64,65,68,69,71,74 and 77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-45,47-50,53,54,57,61-63,66,67,70,72,75 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/12/04;4/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group II in the reply filed on 9/15/06 is acknowledged. The traversal is on the ground(s) that the search and classification for each group will substantially overlap. Applicant has made this assertion without a showing of how there would be substantial overlap and without showing how the restriction requirement was improper. It is the examiners position that the restriction was made without error and further the burden placed on the office to search and examine all of the inventions would be high. Applicants election of species filed 4/12/07 is acknowledged. Applicant traversed the requirement made 12/04/06 by asserting that the search and classification for each species will substantially overlap. Applicant has made this assertion without a showing of how there would be substantial overlap and without showing how the species requirement was improper. It is the examiners position that the species requirement was made without error and further the burden placed on the office to search and examine all of the inventions would be high.

The requirement is still deemed proper and is therefore made FINAL.

Claim1-32, 46, 51, 52, 55, 56, 58-60, 64, 65, 68, 69, 71, 74, 77 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 4/12/07 and 9/16/06.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37, 41-43, and 75 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites "at or near the neovascularization site", claim 41 recites "the site of angiogenesis" and claim 75 recites "wherein the chemotherapeutic agent. . ." None of these terms finds antecedent basis in the context of the claims. Claims 42 and 43 are rejected as they depend from and claim 41.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-45, 53-54, 57, 61-63, 66, 67, 70, 72, 73, 75, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thrue et al [US 2004/0096848], in view of Robinson et al [5,801,156] and Tuschl et al [US 2004/0259247].

The invention is as stated in the rejected claims.

Thrue et al have taught oligomeric compounds for the modulation of HIF-1alpha. It has been taught at paragraph [0005] "It has been demonstrated that engineered down-regulation of HIF-1.alpha. by intratumoral gene transfer of an antisense HIF-1.alpha. plasmid leads to the down-regulation of VEGF, and decreased tumor microvessel density . . ." At paragraph [0024] it has been taught "As used herein, the terms "oligomeric compound" refers to an oligonucleotide which can induce a desired therapeutic effect in humans through for example binding by hydrogen bonding to either a target gene "Chimeraplast" and "TFO", to the RNA transcript(s) of the target gene "antisense inhibitors", "siRNA", "ribozymes" and oligozymes" or to the protein(s) encoding by the target gene "aptamer", spiegelmer" or "decoy"."

This disclosure indicates that although the reference is directed in particular to LNA antisense compounds, one in the art could use any of a number of oligomeric compounds of a class of nucleic acid inhibitors as stated in paragraph [0025], which includes siRNA. For example, see paragraphs [0069] and [0070] where it is stated "For instance, LNA oligomeric compounds may be designed as antisense inhibitors, which are single stranded nucleic acids that prevent the production of a disease causing protein, by intervention at the mRNA level. Also, they may be designed as Ribozymes or Oligozymes which are antisense oligonucleotides which in addition to the target binding domain(s) comprise a catalytic activity that degrades the target mRNA (ribozymes) or comprise an external guide sequence (EGS) that recruit an endogenous enzyme (RNase P) which degrades the target mRNA (oligozymes)

Equally well, the LNA oligomeric compounds may be designed as siRNA's which are small double stranded RNA molecules that are used by cells to silence specific endogenous or exogenous genes by an as yet poorly understood "antisense-like" mechanism. "

At paragraph [0114] it is disclosed that pharmaceutical compositions comprising the oligomeric compounds targeting HIF-1alpha of the invention can be used to treat a variety of diseases such as cancers including retinoblastoma. At paragraph [0130] it is taught "The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be (a) oral (b) pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal,

intranasal, (c) topical including epidermal, transdermal, ophthalmic and to mucous membranes including vaginal and rectal delivery; or (d) parenteral including intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. In one embodiment the active oligo is administered IV, IP, orally, topically or as a bolus injection or administered directly in to the target organ (emphasis added)".

At paragraph [0133] is is taught "Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Delivery of drug to tumour tissue may be enhanced by carrier-mediated delivery including, but not limited to, cationic liposomes, cyclodextrins, porphyrin derivatives, branched chain dendrimers, polyethylenimine polymers, nanoparticles and microspheres (Dass CR. J Pharm Pharmacol 2002; 54(1):3-27). (emphasis added)" .

At paragraphs [0122]-[0123] it has been taught that ligands can be used to to target cells expressing high levels of the ligand target.

At paragraphs [0139] – [142] it has been taught:

Oligonucleotides of the invention may be used to abolish the effects of HIF-1.alpha. induction by acute hypoxia induced by androgen withdrawal therapy in prostate cancer.

[0138] Oligonucleotides of the invention may also be conjugated to active drug substances, for example, aspirin, ibuprofen, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic.

[0139] LNA containing oligomeric compounds are useful for a number of therapeutic applications as indicated above. In general, therapeutic methods of the invention include administration of a therapeutically effective amount of an LNA-modified oligonucleotide to a mammal, particularly a human.

[0140] In a certain embodiment, the present invention provides pharmaceutical compositions containing (a) one or more antisense compounds and (b) one or more other chemotherapeutic agents which function by a non-antisense mechanism. When used with the compounds of the invention, such chemotherapeutic agents may be used individually (e.g. mithramycin and oligonucleotide), sequentially (e.g. mithramycin and oligonucleotide for a period of time followed by another agent and oligonucleotide), or in combination with one or more other such chemotherapeutic agents or in combination with radiotherapy. All chemotherapeutic agents known to a person skilled in the art are here incorporated as combination treatments with compound according to the invention.

[0141] Anti-inflammatory drugs, including but not limited to nonsteroidal anti-inflammatory drugs and corticosteroids, antiviral drugs, and immuno-modulating drugs may also be combined in compositions of the invention. Two or more combined compounds may be used together or sequentially.

[0142] In another embodiment, compositions of the invention may contain one or more antisense compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more additional antisense compounds targeted to a second nucleic acid target. Two or more combined compounds may be used together or sequentially.

At paragraph [0145] it has bee taught:

[0145] Optimum dosages may vary depending on the relative potency of individual oligonucleotides. Generally it can be estimated based on EC50s found to be effective in in vitro and in vivo animal models. In general, dosage is from 0.01 .mu.g to 1 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 10 years or by continuous infusion for hours up to several months. The repetition rates for dosing can be estimated based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state.

Claims 19-36 also provide the following:

19. A pharmaceutical composition comprising the compound of any one of claims 1-18, which further comprises a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising the compound of any one of claims 1-18, which is employed in a pharmaceutically acceptable salt.

21. A pharmaceutical composition comprising the compound of any one of claims 1-18, which further comprises a conjugate or formulation.

22. A pharmaceutical composition comprising the compound of any one of claims 1-18, which constitutes a pro-drug.

23. A pharmaceutical composition comprising the compound of any one of claims 1-18, which further comprises other oligomeric compounds, chemotherapeutic compounds, antiinflamatory compounds and/or antiviral compounds.

24. A method of inhibiting the expression of HIF-1.alpha., in cells or tissues comprising contacting said cells or tissues with the compound according to any one of claims 1-23 so that expression of HIF-1.alpha. is inhibited.

25. A method of modulating expression of a gene involved in a disease comprising contacting the gene or RNA from the gene with an oligomeric compound wherein said compound has a sequence comprising at least an 8 nucleobase portion of SEQ ID NO: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114 or 115 whereby gene expression is modulated.

26. A method according to claim 25, wherein the compounds comprise one or more LNA units.

27. The method of claim 25 or 26, wherein the compound hybridizes with messenger RNA of the gene to inhibit expression thereof.

28. A method of treating a mammal suffering from or susceptible from an cancer disease, comprising: administering to the mammal an therapeutically effective amount of an oligonucleotide targeted to HIF-1.alpha. that comprises one or more LNA units.

29. The method according to any one of claims 25-28 wherein the disease is a common cancer, as e.g. primary and metastatic breast, colorectal, prostate, pancreas, other GI-cancers, lung, cervical, ovarian, brain, head and neck, cervix, colon, liver, thyroid, kidney, testes, stomach, intestine, bowel, esophagus, spinal cord, sinuses, bladder or urinary tract tumors, as well as pre-eclampsia, inflammatory bowel disease and Alzheimers disease.

30. A method of modulating angiogenesis as well as red blood cell proliferation, cellular proliferation, iron metabolism, glucose and energy metabolism, pH regulation, tissue invasion, apoptosis, multi-drug resistance, cellular stress response or matrix metabolism comprising contacting a cell with the antisense compound of claim 1-18 so that the cell is modulated.

31. A method of inhibiting the proliferation of cells comprising contacting cells in vitro with an effective amount of the antisense compound of claim 1-18, so that proliferation of the cells is inhibited.

32. The method of claim 31 wherein said cells are cancer cells.

33. A method of modulating apoptosis in a cell comprising contacting a cell with the antisense compound of claim 1-18 so that apoptosis is modulated.

34. The method of claim 33 wherein said modulation of apoptosis is sensitization to an apoptotic stimulus.

35. The method of claim 33 or 34 wherein said apoptotic stimulus is a cytotoxic chemotherapeutic agent.

36. The method of claim 35 further comprising contacting said cells with a chemotherapeutic agent.

Thrue et al have not specifically taught siRNA of 19-25 size, opsonization moieties, treatment of age related macular degeneration.

Robinson et al have taught that age-related macular degeneration as well as many other neovascular diseases of the eye can be treated with VEGF antisense compounds. Since it was known in the art that the inhibition of HIF-1alpha also inhibits VEGF activity it would have been apparent to one or ordinary skill in the art that HIF-1alpha is also a viable target to treat age related macular degeneration, especially since Thrue et al have taught the inhibition of angiogenesis with HIF-1alpha LNAs, for example.

Tuschl et al have taught siRNA as inhibitors of nucleic acid targets in mammalian cells and have taught the size range 19-25 as a standard siRNA size range, see paragraph [0009], for example.

It is noted that the instant references do not specifically disclose opsonization moieties but it is clear from applicants disclosure that the use of such moieties was well known and routinely used in liposome formulations, see page 19-20, for example.

Since the treatment of diseases such as retinoblastoma and other neovascular diseases or conditions with siRNA were known in the art and since the art has taught all of the limitations of the claimed invention such that one in the art is clearly brought to the claimed invention one would clearly have combined the Thrue et al disclosure to include a specified size range of siRNA and further would have known to target another neovascular disease such as age related macular degeneration.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thrue et al [US 2004/0096848], in view of Robinson et al [5,801,156] and Tuschl et al [US 2004/0259247] as applied to claims 33-45, 53-54, 57, 61-63, 66, 67, 70, 72, 73, 75, 76 above, and further in view of Tuschl, T. [Nature Biotechnology Vol. 20:446-448, 5/2002] and Noonberg et al [US5,624,803].

The invention is as above but where the siRNA is expressed from an viral [AAV] vector.

Tuschl has taught the expression of siRNA from vectors and asserts that the endogenous expression of siRNAs from vectors is thought to overcome some limitations of exogenous siRNA delivery. Tuschl asserts that the use of viral vectors can be advantageous for use in cells refractory to plasmid vectors, for example. The use of vectors to express small RNAs is not new. Noonberg et al have taught for example in vivo nucleotide generators to produce small RNAs in mammals, for example (see claims, for example). It is noted that instant specification appears to admit that it would be routine to select vectors to express siRNA and cites several references at pages 13 and 14 and further at pages 14 –15 there is specific reference to several citations that teach AAV vectors, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Sean R. McGarry/ whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean R McGarry/
Primary Examiner
Art Unit 1635